Remarks

The Amendments

Minor clarifying amendments have been made to independent claims 1 and 71. In claim 1, language from the preamble has been moved to steps (a) and (e). The preamble also has been amended to recite "selecting," which corresponds to "selecting" recited in step (e). Step (e) has been amended to recite "the presence or absence of the polymorphic marker," which corresponds to language present in independent claim 71.

Independent claim 71 has been amended to recite a method of selecting a "personalized" medical intervention, which is supported *inter alia* by the preamble of originally filed claim 1. Step (a) has been amended to recite a polymorphic marker (corresponding to the polymorphic marker recited in step (b)) and to recite a gene "associated with a disorder" (also supported by language in originally filed claim 1).

New dependent claims 77-89 mirror original dependent claims 2-5 and 7-15. New independent claim 90 is supported by claim 71, but recites steps (a)(1) – (a)(4) as active steps; new dependent claims 91-108 are based on original claims 1-20. New independent claim 109 is based on original claim 1 but recites product-by-process steps by which the polymorphic marker is identified; new dependent claims 110-127 are based on original claims 2-5 and 7-20. New independent claim 128 is supported by steps (a)(1) – (a)(4) of claim 71; new dependent claims 129-144 are supported by original claims 2-5 and 8-20.

Information Disclosure Statement

The Office Action states that the list of references in the specification "is not a proper information disclosure statement." Page 2, paragraph no. 4. The list of references at pages 24-27 was not intended to be an information disclosure statement. It is merely a list of the references referred to by number throughout the specification.

Applicants filed an information disclosure statement in a separate paper on July 25, 2001. Applicants respectfully request that the Examiner consider the information in that statement and return an initialed copy of the PTO Form-1449 with the next communication.

Objection to the Specification

The Office Action objects to the specification because "documents have been improperly incorporated by reference." Page 3, paragraph no. 5. Applicants respectfully request clarification of this objection. The only mention of incorporation by reference is in the paragraph beginning on page 17, line 30, which states "All patents and patent applications cited in this disclosure are expressly incorporated herein by reference." No patents or applications are cited in the present specification; thus, none have been improperly incorporated by reference. In any case, this sentence has been deleted. If the Office believes non-patent documents have been improperly incorporated by reference, Applicant respectfully requests that the Office specifically point to such documents in its next communication.

The Rejection of Claims 1-20 and 71-76 Under 35 U.S.C. § 112, first paragraph

Claims 1-20 and 71-76 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse the rejection.

The legal standard for whether a specification meets the enablement requirement of 35 U.S.C. § 112, first paragraph is whether the specification teaches one of skill in the relevant art to make and use the full scope of the claimed invention without the need for undue experimentation. *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993). To determine whether the present specification meets this standard, the claims must first be properly construed. M.P.E.P. § 2164.04. Then, to support a finding of non-enablement of claims 1-20 and 71-76, the Office must establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d at 1562, 27 U.S.P.Q.2d (BNA) at 1513. The Office must not only explain why it doubts the statements in the specification's supporting disclosure, but also must support its assertions "with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370.

In this case, the U.S. Patent and Trademark Office has not met its burden. It has misconstrued the scope of the claims and has not provided a reasonable basis to question the enabling teachings in the specification relevant to the properly construed claims.

Claims 1-20 and 71-76 are directed to methods of selecting personalized medical interventions for non-rodent individuals. As the specification explains,

> With the sequencing of the human genome nearing completion, it will become more and more commonplace to identify genetic mutations which cause a disorder, which predispose an individual

to a disorder, or which may affect an individual's response to a drug and then to tailor a medical intervention for that individual.

Accurate identification of polymorphic markers is essential for this individualized approach to therapy.

Page 1, lines 14-20. Claims 1-20 and 71-76 recite methods of identifying medical interventions suitable for a particular individual based on the presence or absence of a polymorphic marker. Each of claims 1-20 recites steps by which the polymorphic marker is detected:

(a) fusing cells of the non-rodent individual to rodent cell recipients to form non-rodent/rodent cell hybrids;

(b) selecting for fused cell hybrids by selecting for a first selectable marker contained on a rodent chromosome and for a second selectable marker contained on a first non-rodent individual chromosome, to form a population of fused cell hybrids;

(c) detecting among the population of fused cell hybrids a subset of hybrids which are haploid for a second non-rodent individual chromosome which is not the same chromosome as the first non-rodent individual chromosome and which was not selected; and

(d) analyzing said subset of hybrids to detect a polymorphic marker in the at least one gene, in a product of the gene, or in the intergenic region, wherein the gene or intergenic region resides on the second non-rodent individual chromosome.

A medical intervention is selected for the non-rodent individual based on the presence or absence of the polymorphic marker (step (e) of independent claim 1).

Each of claims 71-76 recites assaying a biological sample obtained from a non-rodent individual for a polymorphic marker which is correlated with expression of a gene that is associated with a disease (step (a) of independent claim 71). In step (a), the correlation is determined by a method comprising four steps:

(1) fusing cells of the non-rodent individual to rodent cell recipients to form non-rodent/rodent cell hybrids;

> (2) selecting for fused cell hybrids by selecting for a first selectable marker contained on a rodent chromosome and for a second selectable marker contained on a first non-rodent individual chromosome, to form a population of fused cell hybrids;
>
> (3) detecting among the population of fused cell hybrids a subset of hybrids which are haploid for a second non-rodent individual chromosome which is not the same chromosome as the first non-rodent individual chromosome and which was not selected;
>
> (4) analyzing said subset of hybrids to detect a polymorphic marker in at least one gene or in at least one intergenic region, wherein the gene or intergenic region resides on the second non-rodent individual chromosome.

A medical intervention for the non-rodent individual is selected based on the presence of absence of the polymorphic marker in the biological sample (step (b) of independent claim 71).

The Office Action characterizes the scope of these claims as "tremendous" and as encompassing "the identification of cures for aging, any cancer, and any autoimmune diseases in human, as well as any malady that could possibly afflict any other life form, including plants, reptiles, birds, ruminants, etc." See paragraph no. 7. This characterization is incorrect. The claimed methods are not directed to identifying cures. The methods are directed to selecting from cures for disorders associated with a polymorphic marker. To clarify this point, the word "identifying" has been deleted from claim 1 and replaced with "selecting," as already recited in step (e).

The Office has ignored explicit recitations in independent claims 1 and 71; when these recitation is considered, the scope of claims 1-20 and 71-76 is not as broad as the Office Action asserts. Independent claim 1 explicitly recites that the non-rodent individual is "predisposed to or [has] a disorder associated with at least one polymorphic marker in at least one gene or in at

least one intergenic region." For clarification, this recitation has been moved from the preamble to step (a). Similarly, amended independent claim 71 explicitly recites assaying for "a polymorphic marker which is correlated with expression of a gene associated with a disorder."

The teachings of the specification bear a reasonable relation to the scope of properly construed claims 1-20 and 71-76. The specification teaches how to detect the recited polymorphic marker at page 7, line 3 to page 11, line 11 and in Examples 1-4. Selection of a personalized medical intervention based on detection of a polymorphic marker was well known in the art when the specification was filed, and the specification provides numerous examples of such interventions. For example, personalized medical interventions include the use of HERCEPTIN® to treat metastatic breast cancer patients who overexpress HER2 (page 14, lines 9-10) and the use of tacrine to treat Alzheimer's patients lacking both copies of the ApoE4 gene (page 14, lines 16-21). Other examples of personalized medical interventions include avoiding fluorouracil treatment for breast cancer patients who have a dehydropyrimidine dehydrogenase deficiency (page 14, lines 27-29), avoiding tricyclic antidepressants or selective serotonin reuptake inhibitors in patients who lack the enzyme CYP2D6 (page 15, lines 3-6), and avoiding pravastatin in patients who have high cholesterol and bear a single nucleotide polymorphism associated with prevention of pravastatin metabolism (page 15, lines 9-11).

The specification also teaches that

> Accurate genetic diagnosis of polymorphic markers in a gene or intergenic region which affect peptides, proteins, or other factors involved in the efficacy or bioavailability of drugs is especially useful for identifying an appropriate medical intervention. For example, after a drug is administered, its efficacy and bioavailability depend on numerous proteins with which it interacts, including carrier proteins, metabolizing enzymes, receptors, and transporters. Sadee, *Pharm. Res. 15*, 959-63, 1998;

> Evans & Relling, *Science 286*, 487-91, 1999; Sadee, *B. Med. J. 319*, 1286, 1999; Mancinelli *et al.*, 2000. Such proteins affect the drug's absorption, distribution, metabolism, and excretion. Variations in the enzymes that metabolize a particular therapeutic agent can affect the effective level of the therapeutic agent. It is well known that the activities or levels of various drug-metabolizing enzymes, such as acetyltransferases and sulfotransferases, exhibit genetic polymorphisms. Bullock, 1999. The principal drug metabolizing enzymes are the cytochrome P450 enzymes (*e.g.*, CYP2D6, 3A4/3A5, 1A2, 2E1, 2C9, and 2C19). Mancinelli *et al.*, *AAPS Pharmsci 2*, article 4, 2000. Cytochrome P450 enzymes (CYPs) can both activate (for example, convert codeine to morphine) and deactivate (for example, nicotine to cotinine) drugs.
>
> Differences in drug responses due to genetic differences in proteins that interact with the drugs are well known. Up to a 16-fold variation in plasma levels of phenytoin, an anticonvulsant drug, have been observed in patients who have received the same doses of the drug. This difference is due, at least in part, to the different levels of CYP2D6 in these patients. Bullock, 1999. CYP2C19, which is involved in the metabolism of anxiolytics, such as diazepam, and anti-ulcer drugs, such as omeprazole, is polymorphically expressed. Sagar *et al.*, Gastroenterology 2000 Sep;119(3):670-6. Thus, accurate knowledge of the presence of particular polymorphic markers in an individual can be used to determine appropriate doses of a drug. In addition, if expression levels of particular enzymes are known, those levels can be manipulated to increase the efficacy of a particular drug.

Page 15, line 15 to page 16, line 11. Thus, the specification provides extensive teachings of personalized medical interventions based on the presence or absence of a polymorphic marker.

The Office has not established a reasonable basis to question the teachings of the present specification. In the absence of a reasonable basis to question these presumptively enabling teachings, the Office cannot make a *prima facie* case that claims 1-20 and 71-76 are not enabled. The arguments above apply with equal force to new claims 77-146.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 71-76 Under 35 U.S.C. § 112, second paragraph

Claims 71-76 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse the rejection.

The Office Action asserts that claims 71-76 "provide[] for the use of a correlation but set forth no steps involved in the method. The preamble of independent claim 71 has been amended to delete the recitation "using a correlation between a polymorphic marker and expression or reduced expression of a gene." Amended claim 71 now recites a method of selecting a personalized medical intervention for a non-rodent individual. Claim 71 still sets forth two positive steps of the method: (a) assaying a biological sample for a polymorphism and (b) selecting a medical intervention for the non-rodent individual based on the polymorphism in the biological sample. Thus, claims 71-76 are definite.

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 71-76 Under 35 U.S.C. § 101

Claims 71-76 stand rejected under 35 U.S.C. § 101 as improper method claims. Applicants respectfully traverse the rejection.

The Office Action asserts that claims 71-76 recite a use but set forth no method steps. This is not true. Amended independent claim 71 is directed to a method of selecting a personalized medical intervention for a non-rodent individual. Claim 71 sets forth two steps by which the method is carried out: assaying for a polymorphic marker (step (a)) and selecting a medical intervention for the non-rodent individual based on the polymorphism in the biological sample (step (b)). Thus, claims 71-76 are proper method claims.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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